

FORM 2

THE PATENTS ACT, 1970 (39 of 1970)

COMPLETE SPECIFICATION

[See section 10; rule 13]

**“An improved industrial process for manufacture of Metoprolol
base and salts thereof”**

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The following specification describes the nature of the invention and the manner in which it is to be performed:

An improved industrial process for manufacture of Metoprolol base and salts thereof

Technical Field of the invention:

This invention relates to an improved industrial process for manufacture of β -blocker, antihypertensive compounds more particularly Metoprolol base and salts thereof.

Background and Prior Art:

Metoprolol and its salts such as tartrate and succinate are well established drugs having anti-hypertensive activity. These compounds acts as β -blockers. The patients suffering from hypertension needs to be on treatment by these drugs for the whole lifetime. This kind of therapy necessitates that; the drugs are of high purity with very less impurity levels, so that the side effect is minimum. It also demands to produce these drugs at cheaper prices.

Ample literature is available for producing metoprolol base and its salts, due to the significance of these compounds as anti hypertensive agents.

Spanish patent ES 2011584 (equivalent US Patent 5082969) describes a process for metoprolol, where 4-(2-methoxyethyl) phenol and epichlorohydrin are reacted in aqueous alkaline conditions at 0° - 25°C temperature for 15-20 hours. The organic phase consisting of epoxide is separated, washed with water and used as such for reaction with large excess of isopropylamine in aqueous media like water at 0° - 30°C temperature.

Polish Patent PL 158497 describes a process wherein 4-(2-methoxyethyl) phenol and epichlorohydrin are reacted at 20° - 80°C temperature for 3 hours under aqueous alkaline conditions. The epoxide so formed is reacted with large excess of isopropyl amine

(medium as well as reactant) to yield metoprolol base.

Nearest prior art to the present invention is the form of US Patent 6252113, discloses reaction between 4-(2-methoxyethyl) phenol and epichlorohydrin in aqueous alkaline conditions at 50° - 70°C temperature for 1 hour. The resulting epoxide is distilled under high vacuum to improve quality. Pure epoxide then is treated with isopropylamine in solvent such as isopropyl alcohol.

As has been seen, lot of knowledge in the present field of invention is available; however, there remain some problems, which lead the scope for further investigations. It can be seen that almost all prior art have reactants per se same. Reactions which are carried out at lower temperatures (below ambient) leads to slow rate of reaction with more impurity levels when the reaction at higher temperature range is carried out, the rate of reaction increased but required purification by distillation under high vacuum.

In the processes where purification of epoxide is avoided, the resultant products are formed with higher impurities. The processes involving excess use of isopropyl amine leads to increased costs. The products formed with higher impurity levels necessitate extra purifications, which enhances the costs.

Therefore, it is of importance to develop a process for manufacture of metoprolol base, which is economical, eco-friendly and yielding high quality with higher yields, which also avoids the operations like high vacuum distillation.

The patients suffering from hypertension needs to be on treatment by these drugs for the whole lifetime. This kind of therapy necessitates that; the drugs are of high purity with very less impurity levels, so that the side effects are minimum. It also demands to produce these drugs at cheaper prices.

Objectives:

The objective of the present invention is to develop a process for manufacture of Metoprolol base and salts thereof, in high yields with higher purity and better operator friendly operations at cheaper prices.

Summary of the Invention:

This invention relates to an improved industrial process for manufacture of β -blocker, antihypertensive compounds more particularly Metoprolol base and salts thereof.

Detailed Description:

The present invention has made possible to produce metoprolol base and its salts in higher yields with high purity and avoiding processes like high vacuum distillation, at cheaper costs.

The present invention involves optimization of reaction temperatures, molar ratio of reactants in order to achieve higher purity and yields by avoiding purification of epoxide intermediates.

The present invention process involves three steps. In the first step is for preparation of epoxide by reacting 4-(2-methoxyethyl) phenol with epichlorohydrin in an aqueous media containing inorganic base such as sodium hydroxide at 40-45°C temperature.

The resultant epoxide is used in the second step for preparation of metoprolol base. The epoxide is treated with isopropylamine in aqueous media to obtain Metoprolol base of high purity in high yields. The last step is converting metoprolol base into the succinate and tartrate salts by reacting with acids like succinic acid or tartaric acid in solvent media such as acetone.

By following the present invention as described below, it has been made possible to produce metoprolol base and its salts in higher yields with high purity and avoiding processes like high vacuum distillation, at cheaper costs.

The present invention involves optimization of reaction temperatures, molar ratio of reactants in order to achieve higher purity and yields by avoiding purification of epoxide intermediates.

It involves three steps :

Step- I : Epoxide formation by reacting 2-(methoxyethyl) phenol with epichlorohydrin.

Step-2 : Metoprolol base from reaction of epoxide with isopropyl amine.

Step- 3 : Metoprolol salts from metoprolol base

The process of the present invention is illustrated by the following example.

Step- I : Epoxide formation :

4-(2-methoxyethyl) phenol and epichlorohydrin are reacted in aqueous media like water, in presence of inorganic base such as sodium hydroxide, at temperature range of 40° - 45°C in 3 to 5 hours time.

The molar ratio of 4-(2-methoxyethyl) phenol to epichlorohydrin used in the range of 1 : 0.92 to 1 : 2.0, wherein the more preferred ratio is 1 : 1.1 to 1 : 1.4 and the most preferred ratio is 1 : 1.31.

Most preferred concentration of sodium hydroxide in water is 25% w/v

Preferred molar ratio of sodium hydroxide to 4-(2-methoxyethyl) phenol used is 1.14 : 0.95, more preferred is 1.024 : 1 and the most preferred ratio is 1.136 : 1

Reaction is carried out in the temperature range of 10° to 45°C, where in most preferred is 40° to 45°C.

Most preferred ratio of 4-(2-methoxyethyl) phenol : water is 1 : 1.6 volumes.

At the end of reaction, aqueous and organic phases are separated out.

The organic phase is washed thrice by water. The pH of washing must be in the range of 7 to 8. This pH range is necessary to achieve high purity of the epoxide.

Traces of water are removed from organic phase by distillation under vacuum below 55°C temperature. Keep the residue at 55°C, under vacuum for 3 to 5 hours, till the purity of sample is achieved in the range of 96-98%

The yield of the epoxide, so obtained is in the range of 93-95% of stoicheometric and purity 97-99%.

The epoxide with above purity is used for making metoprolol base.

Step-2 : Metoprolol base

The epoxide and isopropyl amine are reacted in aqueous media like water at temperature 0° - 30°C.

Preferred temperature during addition of epoxide is 10° to 25°C, while the most preferred temperature for completion of reaction is 30°C

Reaction completes in 3 hours time at 30°C.

Preferred molar ratio of epoxide : isopropyl amine is 1 : 5.0 – 5.5 where in the most preferred ratio is 1 : 5.2 - 5.3

Ratio of water to epoxide is 2 : 1 vol. : wt.

On completion of reaction, the reaction mixture is cooled to 0° – 5°C.

In order to achieve high purity it is necessary to maintain above temperature range. Formation of impurity at RRT 0.35 (By GC) is minimized by operating at 0° - 5°C. It is observed that in cases temperature rises above the range, this impurity increases.

The reaction mass is quenched by 2.25 volume of water. The product is extracted by 3 volumes of toluene. The toluene layer is washed three times by water for removal of isopropyl amine content is less than 0.5%.

Traces of isopropyl amine are removed by maintaining under vacuum below temperatures 25°C. It is necessary to eliminate traces of isopropyl amine at low temperature below 25°C, as the presence of isopropyl amine during distillation of toluene above 25°C leads to the formation of an impurity at RRT 1.54 by (GC). Following the present invention process this impurity formation is avoided.

In case when isopropyl amine remained in the traces, the impurity at RRT 1.54 (by GC) is detected.

Thus, following process as per present invention, formation of the impurities at RRT 0.35 & RRT 1.54 are under control, which leads to yield highly pure Metoprolol base in higher yields.

The analysis of sample of toluene layer shows absence of isopropyl amine. Toluene is distilled out at temperature 30° - 40°C under vacuum.

The residue of metoprolol base so obtained shows purity more than 99% and the yield of which is in range of 88 to 89%. (Stoicheometric)

Step- 3 : Metoprolol salts from metoprolol base

Metoprolol succinate :

Metoprolol base was converted to Metoprolol succinate, by reacting with succinic acid. The metoprolol base was dissolved in solvent such as acetone, at the temperature of $45\pm 2^{\circ}\text{C}$. The succinic acid used in solution form the solution of succinic acid was prepared by refluxing in acetone. The succinic acid was used in stoichiometric proportion of 2 moles : 1 mole of metoprolol base.

The solution of succinic acid was added to the solution of metoprolol base. After mixing of the solution, pH of the reaction mass was adjusted 7.1 to 7.3. The reaction was carried out by refluxing for 4-5 hours. Then reaction mass was cooled to the temperature of $25\pm 2^{\circ}\text{C}$ and stirred at the temperature, followed by filtration. The metoprolol succinate so obtained was purified by crystallization from methanol.

Metoprolol succinate obtained with the yield of 72-75% (stoichiometric) having purity of more than 99.8% by HPLC and any other impurity less than 0.1%.

Metoprolol tartrate :

The metoprolol base was reacted with tartaric acid to obtain metoprolol tartrate salt. Metoprolol base was dissolved in suitable solvent such as acetone, at the temperature of $45\pm 2^{\circ}\text{C}$. Tartaric acid was dissolved in solvent like acetone under refluxing conditions. The tartaric acid used in the molar ratio of 1 : 2 moles of metoprolol base. The solution of tartaric acid was added to the solution of metoprolol base and the pH was adjusted between 6.1 to 6.3

Reaction was refluxed for 4 hours for completion of salt formation, then cooled and stirred at $25\pm 2^{\circ}\text{C}$ for 2 hours. Metoprolol tartrate was obtained by filtration, which was then purified by crystallization from solvent like isopropanol. The metoprolol tartrate

obtained in the yield of 72-73% (stoichiometric) with purity of more than 99.8% and any other single impurity NMT 0.1%

EXAMPLES: METOPROLOL BASE FORMATION:

STEP – I: Epoxide preparation:

Example – 1:

200 gm (1.31 mole) 4 -(2 – methoxy ethyl) phenol was reacted with 159.45 gm (1.72 mole) epichlorohydrin, in presence of sodium hydroxide 59.80 gm (1.49 mole) in 320 ml water. The reaction mass was heated to 40 – 45°C for 5 – 6 hours. At the end of reaction, the aqueous phase was separated and the organic phase was washed with water to bring pH in the range of 7 – 8. The traces of water were removed by distillation under vacuum below 55°C. The epoxide was maintained under vacuum below 55°C temperature for 3 – 5 hours to get the purity in the range of 96 – 98%. The yield of Epoxide obtained is 254 – 260 gm (93 - 95%) with purity of 97 – 99% by HPLC.

Example – 2:

200 gm (1.31 mole) 4 -(2 – methoxy ethyl) phenol was reacted with 170.40 gm (1.84 mole) epichlorohydrin, in presence of sodium hydroxide 59.80 gm (1.49 mole) in 320 ml water. The reaction mass was heated to 40 – 45°C for 5 – 6 hours. At the end of reaction, the aqueous phase was separated and the organic phase was washed with water to bring pH in the range of 7 – 8. The traces of water were removed by distillation under vacuum below 55°C. The epoxide was maintained under vacuum below 55°C temperature for 3 – 5 hours to get the purity in the range of 96 – 98%. The yield of Epoxide obtained is 240 – 246 kg (88 - 90%) with purity of 97 – 99% by HPLC.

Example – 3:

200 gm (1.31 mole) 4 -(2 – methoxy ethyl) phenol was reacted with 121.71 gm (1.31 mole) epichlorohydrin, in presence of sodium hydroxide 53.89 gm (1.34 mole) in 320 ml water. The reaction mass was heated to 40 – 45°C for 5 – 6 hours. At the end of reaction, the aqueous phase was separated and the organic phase was washed with water to bring

pH in the range of 7 – 8. The traces of water were removed by distillation under vacuum below 55°C temperature. The epoxide was maintained under vacuum below 55°C temperature for 3 – 5 hours to get the purity in the range of 96 – 98%. The yield of Epoxide obtained is 218 – 232 kg (80 - 85%) with purity of 97 – 99% by HPLC.

Example – 4:

200 gm (1.31 mole) 4 -(2 – methoxy ethyl) phenol was reacted with 159.45 gm (1.72 mole) epichlorohydrin, in presence of sodium hydroxide 59.80 gm (1.49 mole) in 320 ml water. The reaction mass was heated to 30 – 35°C and maintained for 17 hours. At the end of reaction, the aqueous phase was separated and the organic phase was washed with water to bring pH in the range of 7 – 8. The traces of water were removed by distillation under vacuum below 55°C. The epoxide was maintained under vacuum below 55°C temperature for 3 – 5 hours to get the pure epoxide. The yield of Epoxide obtained is 213 gm (78 %) with purity of 82.57% by HPLC.

STEP – II: Metoprolol Base Preparation

Example – 1:

250 gm (1.20mole) Epoxide (from example-1 step – I) was added in the solution of 355 gm (6.01 mole) iso propyl amine in 500 ml water at 10°C temperature. The reaction was maintained further at 30°C for three hours. After cooling the reaction mass to 10 – 15°C, was quenched in 565 ml of water. The product was extracted in toluene (750 ml). The toluene layer was washed with water to remove excess of iso propyl amine and bring the limit of iso propyl amine below 0.5%. Traces of iso propyl amine were removed under vacuum below 25°C. The toluene layer was concentrated under vacuum at 30 – 40°C. The yield of metoprolol base was 282 – 285 gm (88 – 89%) with purity of 99% by HPLC.

Example – 2:

225 gm (1.08 mole) Epoxide (from example-2 step – I) was added in the solution of 351 gm (5.95 mole) iso propyl amine in 450 ml water at temperature of 10°C. The reaction was maintained further at 30°C for three hours. After cooling the reaction mass to 10 –

15°C, was quenched in 506 ml of water. The product was extracted in toluene (675 ml). The toluene layer was washed with water to remove excess of iso propyl amine and bring the limit below 0.5%. Traces of iso propyl amine were removed under vacuum below 25°C. The toluene layer was concentrated under vacuum at 30 – 40°C. The yield of metoprolol base was 254 – 257 kg (88 – 89%) with purity of 97 – 99% by HPLC.

Example – 3:

225 gm (1.08 mole) Epoxide (from example-3 step – I) was added in the solution of 319.10 gm (5.00 mole) iso propyl amine in 450 ml water at temperature of 10°C. The reaction was maintained further at 30°C for three hours. After cooling the reaction mass to 10 – 15°C, was quenched in 506 ml of water. The product was extracted in toluene (675 ml). The toluene layer was washed with water to remove excess of iso propyl amine and bring the limit below 0.5%. Traces of iso propyl amine were removed under vacuum below 25°C. The toluene layer was concentrated under vacuum at 30 – 40°C. The yield of metoprolol base was 245 – 251 kg (85 – 87%) with purity of 97 – 99% by HPLC.

STEP - III: SALT FORMATION:

Example – 1:

267 gm metoprolol base (from example-1 step – II) was dissolved in 1870 ml of acetone and heated to 45°C. After charcoalisation and filtration at 45°C, the reaction mass was heated to reflux. Adjust the pH of the reaction to 7.1 – 7.3 using succinic acid solution prepared by dissolving 59.045 gm succinic acid in 1140 ml acetone at reflux. Maintain the reaction at reflux for 4 hours. Cool the reaction to 26°C and maintain 2 hours. The precipitated salt was filtered to get crude metoprolol succinate. The crude product was purified by crystallization in 800 ml methanol. The filtered product was dried to yield 277 – 288 gm (72 – 75 %) with purity of more than 99.8% by HPLC and any other impurity less than 0.1%.

Example – 2:

267 gm metoprolol base (from example-1 step – II) was dissolved in 1870 ml of acetone and heated to 45°C. After charcoalisation at 45°C for 30 minutes and filtration, the reaction mass was heated to reflux. Adjust the pH of the reaction to 6.1 – 6.3 using tartaric acid solution prepared by dissolving 75.045 gm tartaric acid in 1350 ml acetone at reflux. Maintain the reaction at reflux for 4 hours. Cool the reaction to 26°C and maintain 2 hours. The precipitated salt was filtered to get crude metoprolol tartrate. The crude product was purified by crystallization in 2400 ml iso propyl alcohol. The filtered product was dried to yield 300 – 305 gm (72 – 73 %) with purity of more than 99.8% by HPLC and any other impurity less than 0.1%.